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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,579	09/07/1999	SUSUMU IKEHARA	Q55691	2802

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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	19

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/380,579	Applicant(s) IKEHARA ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,10 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 September 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 4/29/02 (Paper No. 18), is acknowledged.
Claim 11 has been cancelled. Claims 1-8 have been canceled previously.
Claim 9 has been amended.

Claims 9-10 and 12 *are pending and under consideration in the instant application.*

2. This Office Action will be in response to applicant's arguments, filed 4/29/02 (Paper No. 18). The rejections of record can be found in the previous Office Action (Paper No. 17).

3. Applicant's cancellation of claim 11 has obviated the previous objections and rejections with respect to this claim.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 9-10 and 12 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's argument, filed 4/29/02, that the term "immunological tolerance" is well-known and used by those skilled in the art, as evidenced by providing a PubMed search using this term, is acknowledged.

However, the Examiner maintains that while the term is used in the art, it usage is imprecise. The metes and bounds of "immunological tolerance" are not established by the mere fact that the term is used in the art. Neither does the specification appear to establish the metes and bounds of the phrase "immunological tolerance".

The rejection is maintained.

It is again suggested that Applicant either identify a definition of the metes and bounds of this phrase that is supported in the specification as filed; or alternatively amend the claims to recite definite language that is supported by the specification.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

6. The previous rejection of claims 9-10 under 35 U.S.C. 102(b) as being anticipated by Ildstad (US Pat. No. 5,514,364, of record) is withdrawn in view of Applicant's amendment, file 4/29/02, incorporating the limitation of claim 11 into independent claim 9.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 9-10 and 12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ildstad (US Pat. No. 5,514,364, of record) in view of Zhang et al. (Eur. J. Immunol. 24 :1558-1565, IDS).

Applicant's arguments, filed 4/29/02, have been fully considered, but have not been found convincing for the reasons of record in Paper No. 18.

The rejection of record may be found in full in Paper No. 18 and is hereby reiterated. Sections of the rejection of record are reiterated below to address Applicant's arguments.

The claims are drawn to a method comprising administering to an organ transplant recipient total body sublethal irradiation of at least 6.5 Gy or 6.5 Gy to 7.0 Gy; and administering whole bone marrow cells by hepatic portal administration; the method optionally further comprising transplanting the organ within the same day as the bone marrow administration.

Applicant argues that Ildstad does not teach the administration of whole bone marrow. Applicant points to column 7 at line 48 to column 8 at line 5, in particular column 7 at lines 60-62, and also to column 16 at lines 59-61 and argues that Ildstad teaches administering T cell depleted (TCD) marrow.

However, the statements pointed to by Applicant are a discussion by Ildstad of approaches used in the art that have resulted in mixed chimerism and are not an indication that T cell depleted marrow was used by Ildstad in the teachings of the '364 patent.

The comment at column 7, lines 60-62 is the second of two approaches, and it is acknowledged that the second approach known in the art does use TCD bone marrow. Similarly, column 16 at lines 59-61 is a comment by Ildstad on the approach taken "in other studies" (column 16 at line 58). The Examiner has carefully reviewed the teachings of Ildstad in the '364 patent and does not find a statement that the bone marrow used in the experiments described was TCD marrow. Further, the fact that Ildstad is careful to point out that other approaches used TCD marrow without indicating T cell depletion of the bone marrow used in the experiments described in section 6.2 "Results" (columns 16-23) is further support that it is not simply that the reference is silent as to whether or not the bone marrow was T cell depleted. Rather, Ildstad clearly appreciated that in some methods of generating mixed chimeras T cell depleted bone marrow was used, but did not use T cell depleted marrow for the experiments described.

Applicant further argues that Ildstad does not teach the level of engraftment of transplanted organs, noting that the column 17 at lines 4-25 are in reference to the engraftment rate of the transplanted bone marrow.

The Examiner agrees that column 17 at lines 4-25 is in reference to engraftment of the bone marrow. However, the Examiner did not point to this location for support that the reference teaches organ grafting. Rather the Examiner previously noted:

> Ildstad further teaches transplantation of organs to the bone marrow recipient and exemplifies skin transplantation, showing that the recipients are specifically tolerant of the donor-type skin (see e.g., Abstract and columns 21-22).

Applicant further comments that the technique used by Ildstad results in a progressive loss of donor bone marrow cells with the result that transplanted organs are then rejected. Applicant points to Figure 1 of Hayashi et al. (Stem Cells 2000; 18:273-280) and Takao et al. (Immunobiol. 1995; 194:376-389) for support for this statement.

First it is noted that Ildstad shows in Figure 7 survival of skin grafts for at least 30 days, which is as long as the animals were monitored. It is further noted that even had the grafts been rejected at day 30 (as noted, the grafts were not rejected); in view of the indefiniteness of the term "immunological tolerance" as set forth supra, graft survival of only 30 days would still have met this limitation given its broadest reasonable interpretation.

With respect to the references cited, the experiments described by Hayashi et al. and Takao et al. can not be used to infer anything about the survival of the transplanted bone marrow in the experiment of Ildstad. Hayashi et al. and Takao et al. use a different experimental procedure to condition the recipient - lethal irradiation (10 Gy [Hayashi] or 9.5 Gy [Takao]) and T cell depleted bone marrow transplantation.

It is again noted that:

> Ildstad teaches and claims a method of conditioning a recipient intended for organ grafting by subjecting the recipient to sublethal total body irradiation and administering to the recipient whole bone marrow (see entire document, but especially the claims and columns 5, 8, 17 and 21-22).
>
> Ildstad also teaches that bone marrow engraftment after sublethal total body irradiation is reliably achieved in 100% of recipients at 7 Gy (see Figure 1 and column 17, especially lines 4-25).
>
> Ildstad further teaches transplantation of organs to the bone marrow recipient and exemplifies skin transplantation, showing that the recipients are specifically tolerant of the donor-type skin (see e.g., Abstract and columns 21-22).

Ildstad does not teach hepatic portal vein administration of the whole bone marrow, nor does she teach transplanting an organ within the same day as administration of the bone marrow.

Applicant argues that Zhang et al. does not make up for these deficiencies because Zhang et al. merely teach a technique which gives rise to a low engraftment rate of transplanted skin.

However, as was previously noted:

> Zhang et al. teach that in both intravenous and portal vein injections of bone marrow cells (BMC), most of the cells migrate to the liver, although more BMC do so after portal vein administration than after intravenous administration (see entire document, especially Figures 3 and 5 and page 1563 at the 4th full paragraph).
>
> Zhang et al. also review the art recognized prolongation of organ graft survival in a recipient when cells from the donor are administered to the recipient via the portal vein in addition to the transplanted organ, and note that this is due to a form of immunological tolerance (see especially the "Introduction" on page 1558 and the 1st paragraph of "Discussion" on page 1563).

Thus the Examiner maintains that given the teachings of Zhang et al. that prolonged organ graft survival was known to be achieved when donor cells were also administered via the hepatic portal vein, one of ordinary skill in the art would have found it obvious to modify the teachings of Ildstad to administer the bone marrow cells by hepatic portal venous administration. One of ordinary skill in the art at the time the invention was made would have been motivated to combine sublethal irradiation and administration of the bone marrow cells via the hepatic portal vein to provide an improved method for inducing immunological tolerance in an organ transplantation recipient. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

Given the teachings of Ildstad and Zhang et al., one of ordinary skill in the art would have reasonably expected that combining two art-recognized approaches for inducing immunological tolerance would have also resulted in a method of inducing immunological tolerance in an organ transplantation recipient. Finally, given the art recognized time constraints associated with transplanting cells and organs from the same human donor; one of ordinary skill in the art would have also been motivated to transplant the organ within the same day as the whole bone marrow cells.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is maintained for the reasons of record in Paper No. 18. Applicant's amendment to place the dependent limitation of now cancelled claim 11 into the body of claim 9 does not affect the rejection of record.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
July 29, 2002

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7/29/02